

Analysis of contributing factors influencing thromboembolic events after total knee arthroplasty

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Background: Venous thromboembolic events (VTE) are a known and well-described complication following total knee arthroplasty (TKA). We sought to validate the American College of Chest Physicians thromboprophylaxis recommendations after elective TKA, paying special attention to our dose adjustments for weight, and their impact on VTE in our population.

Methods: We retrospectively investigated risk factors in patients undergoing TKA, focusing mainly on symptomatic VTE occurrence rates from deep vein thrombosis (DVT) or pulmonary embolism (PE). The anticoagulation protocol consisted of starting low molecular weight heparin (LMWH) therapy, with dalteparin administered 12 h after surgery in patients who received general anesthesia or 24 h later in patients who received single-dose regional anesthesia.

Results: Data from 346 patients (mean age 66.8 [range 24–91] yr) who underwent primary or revision TKA depicted an overall symptomatic VTE rate of 15%. The proximal DVT rate was 1.7%, and the nonfatal PE rate was 0.9%. The mean time to VTE diagnosis was 5.6 days. The first dalteparin dose was administered 19.5 (range 10–48) h after surgery in patients without VTE and 22.6 (range 11.5–52) h after surgery in patients with VTE ($p = 0.003$). With a first dose of dalteparin administered 12 h postoperatively, patients presented significantly lower DVT and PE rates than if it was administered 24 h postoperatively (8.5% v. 16.3%, $p = 0.048$).

Conclusion: Delayed administration of LMWH has deleteriously impacted the VTE rate after TKA at our institution. Prompt initiation of LMWH (≤ 12 h after surgery) is appropriate, without increasing the risk of major bleeding.

Contexte : Les événements thromboemboliques veineux (ETV) sont une complication connue et bien décrite de la chirurgie pour prothèse totale du genou (PTG). Nous avons voulu valider les recommandations de l'American College of Chest Physicians en matière de thromboprophylaxie après la PTG non urgente en portant une attention particulière à l'ajustement des doses selon le poids et à leur impact sur les ETV dans notre population.

Méthodes : Nous avons analysé de manière rétrospective les facteurs de risque chez des patients soumis à une PTG en nous attardant principalement aux taux d'ETV symptomatiques sous forme de thrombose veineuse profonde (TVP) ou d'embolie pulmonaire (EP). Le protocole d'anticoagulothérapie prévoyait l'administration d'une héparine de bas poids moléculaire (HBPM), la dalteparine, 12 h après la chirurgie chez les patients ayant reçu une anesthésie générale, ou 24 h après chez les patients ayant reçu une anesthésie locorégionale à dose unique.

Résultats : Les données provenant de 346 patients (âgés en moyenne de 66,8 ans [éventail 24-91 ans]) ayant subi une PTG primaire ou une révision de PTG ont révélé un taux d'ETV symptomatique global de 15 %. Le taux de TVP proximal a été de 1,7 % et le taux d'EP non fatale a été de 0,9 %. Le temps moyen avant le diagnostic d'ETV a été 5,6 jours. La première dose de dalteparine avait été administrée 19,5 h (éventail 10-48 h) après la chirurgie chez les patients n'ayant pas présenté d'ETV et 22,6 h (éventail 11,5-52 h) après la chirurgie chez les patients ayant manifesté un ETV ($p = 0,003$). Avec une première dose de dalteparine administrée 12 h après l'intervention, les patients ont présenté des taux de TVP et d'EP significativement moindres que si elle leur avait été administrée 24 h après l'intervention (8,5 % c. 16,3 %, $p = 0,048$).

Conclusion : L'administration retardée de l'HBPM a produit des effets défavorables pour ce qui est des taux d'ETV après la PTG dans notre établissement. L'instauration rapide de l'HBPM (≤ 12 h après la chirurgie) est appropriée et n'accroît pas le risque d'hémorragie majeure.

The occurrence of venous thromboembolic events (VTE) following total knee arthroplasty (TKA) is a known and well-described complication. Without thromboprophylaxis, the rate of symptomatic and asymptomatic deep vein thrombosis (DVT) detected by venography following reconstructive knee surgery is 41%–84%, with proximal events presenting 5%–22% of the time.¹ Pulmonary embolism (PE) is less frequent, with rates of 1.5%–10%, but it is associated with a mortality of 0.1%–1.7%.¹ With appropriate thromboprophylaxis, the rate of symptomatic and asymptomatic DVT detected by venography or Doppler ultrasonography is 25.6%–38.1%, and the rate of proximal events is 1.3%–5.7%.^{2,3} With prophylaxis and considering only symptomatic VTE, the event rate is low but will not reach zero; the incidence of symptomatic VTE usually varies between 0.6% and 5.7%, that of DVT proximal to the knee varies between 0.33% and 2.1%, and that of PE varies between 0% and 1%.^{1–9} Previous studies present a wide range of disparity in the nature of the thromboprophylactic agent used, the hospital length of stay, the rehabilitation protocol and the duration of thromboprophylaxis.

Practice guidelines have been proposed by different scientific societies. The American College of Chest Physicians (ACCP) recommended that all patients undergoing TKA have thromboprophylaxis (low molecular weight heparin [LMWH], fondaparinux, or adjusted-dose vitamin K antagonist) for a minimum of 10 days after surgery. When using LMWH, the ACCP suggests giving the first dose either before or after surgery.^{1,10} On the other end of the spectrum, the American Academy of Orthopaedic Surgeons (AAOS) recommends thromboprophylaxis only if the patient is at risk for PE (previous VTEs, hereditary thrombophilia, hypercoagulable state or late mobilization after surgery). Acetylsalicylic acid (ASA), LMWH, fondaparinux, warfarin or no agents are among the choices recommended by the AAOS according to risk levels.^{10,11}

The present study was conducted to validate the ACCP thromboprophylaxis recommendations after elective TKA, paying special attention to our dose adjustments for weight, and their impact on VTE in our population compared with current literature. We also sought to identify risk factors specific to our patient characteristics, the thromboprophylaxis used and the surgical technique used.

METHODS

All patients undergoing elective primary TKA or revision TKA at our university-affiliated hospital between May 1, 2008, and Apr. 30, 2010, were potentially eligible to participate in the study. All patients who received thromboprophylaxis with dalteparin at a prophylactic dose for a period of 14 days after surgery in the reconstructive orthopaedic surgery unit constituted the study population. However, in patients heavier than 100 kg, the

LMWH dose has been historically, but not systematically, increased by 50% in certain individuals at our institution, depending on the pharmacist's opinion. Patients with a therapeutic dose of dalteparin (200 units/kg/d) or taking warfarin, fondaparinux, danaparoid, lepirudin, argatroban or other LMWH were excluded. The study received institutional approval and was conducted without contacting patients.

The primary outcome of the study was the rate of occurrence of symptomatic VTE, whether a DVT or PE, confirmed by objective testing during the 90-day postoperative period. DVT was diagnosed by means of Doppler ultrasonography, and PE was diagnosed with CT angiography and/or lung ventilation/perfusion scans. A retrospective systematic chart review was conducted to gather patient characteristics (age, sex, weight, height), thromboprophylaxis protocol (dosage of dalteparin, the anti-Xa levels when measured, the time between surgery and first dose of dalteparin) and surgical data (presence and duration of tourniquet, surgical technique, anesthesia type, the use of tranexamic acid in the perioperative period, primary v. revision TKA, blood transfusion of more than 2 units of packed red blood cells [PRBCs], a decrease of more than 2 g/dL in hemoglobin [Hb]). Specific risk factor assessment included a previous history of VTE, hormone therapy before surgery, active cancer in the last 6 months, thrombophilia and the interruption of LMWH before the 14th postoperative day. We collected the number of Doppler, CT angiography or lung ventilation/perfusion scans performed in the first 3 postoperative months in our centre. No routine screening tests for asymptomatic DVT or PE were performed at hospital discharge over the course of the study period.

Since 2007, thromboprophylaxis used at our institution following TKA has been almost exclusively dalteparin. The first dalteparin dose was administered 12 h after surgery in patients undergoing general anesthesia and 24 h later when single-dose regional anesthesia was preferred, or as otherwise specified by the orthopedic surgeon after closing the wound, mostly pertaining to subjective bleeding risks. The dalteparin treatment may have been interrupted over the 14 postoperative days in the presence of active bleeding, knee hemarthrosis, acute drop (> 2 g/dL) in Hb, or abnormal wound drainage, as defined at the discretion of the surgeon. A universal dalteparin dosage of 5000 units/d was prescribed with a downward or upward adjustment when body weight did not reach 45 kg or exceeded 100 kg. Anti-Xa level after the third dose of dalteparin was customarily assessed to make dosage adjustments when required under the supervision of the hospital pharmacist.

Statistical analysis

The aim of the study was to calculate the rate of occurrence of a symptomatic VTE in our population and to

identify patient, pharmacological, surgical, or thromboprophylaxis characteristics that were predictive of VTE. Baseline quantitative variables are described using means and standard deviations (SD) and compared using Student *t* tests. Baseline categorical variables were analyzed using χ^2 or Fisher exact tests, as required. When assessing results, we compared the variables of patients with and without VTE using χ^2 , Fisher exact, or Student *t* test, as required. Logistic regression analysis was used to evaluate the association between VTE and predictor variables of interest. These variables are reported as odds ratios (OR) with associated 95% confidence intervals (CI). For all analyses, differences were considered significant at $p < 0.05$. Statistical analysis was performed using SPSS version 11.0 (SPSS Inc.). Data are expressed as means \pm SD, unless otherwise specified.

RESULTS

Between May 1, 2008, and Apr. 30, 2010, 371 patients underwent primary and revision TKA, of whom 25 were excluded for meeting 1 or more of the exclusion criteria (Fig. 1), leaving 346 patients for inclusion in the study. The mean age at surgery was 66.8 ± 10.2 (range 24–91) years, most patients (216; 62%) were women, and the mean body mass index (BMI) was 32.3 ± 6.3 (range 18–56). Patient characteristics are found in Table 1. The number of patients with a known history of thrombophilia or active cancer in the last 6 months has not been analyzed, given the small number of patients involved.

The multivariate analysis between age, sex and body weight in patients experiencing a VTE did not highlight any associations. Data on Anti-Xa level were available for 88 of 346 patients; 0% (0 of 12 patients) in the VTE group and 11% (8 of 76 patients) in the no VTE group required a dalteparine dose increase during the course of their hospital stay. Further analysis showed a nonsignificant association between low levels of Anti-Xa and VTE.

The overall VTE rate was 15%, with a majority (11.0%) being distal DVT (Table 2). The rate of proximal DVT was 1.7%, and the rate of nonfatal PE was 0.9%. Two patients experienced both a DVT and a PE. Doppler ultrasonography was requested in 34.7% of patients before hospital discharge based on calf pain and swelling as reported by patients, and only 42.5% of the scans were positive. Indication for lung ventilation perfusion scans or CT pulmonary angiography included shortness of breath and/or pulse oxymetry desaturation upon exertion when mobilizing the patient. The mean time to diagnosis of VTE in our study was 5.6 days, and if only DVT is considered, the time to diagnosis was 5.0 days. History of VTE was not a significant risk factor for a VTE developing ($p = 0.15$). The continuation of hormone replacement therapy 4 weeks before surgery was identified as a potential risk factor (OR 2.4, 95% CI 0.85–6.89). The mean length of stay in patients without VTE was 8.2 ± 3.5 (range 3–33) days and was prolonged for a mean of 3 additional days with the development of VTE ($p < 0.001$). This data set represents a period before the establishment of a fast-track care pathway for TKA in

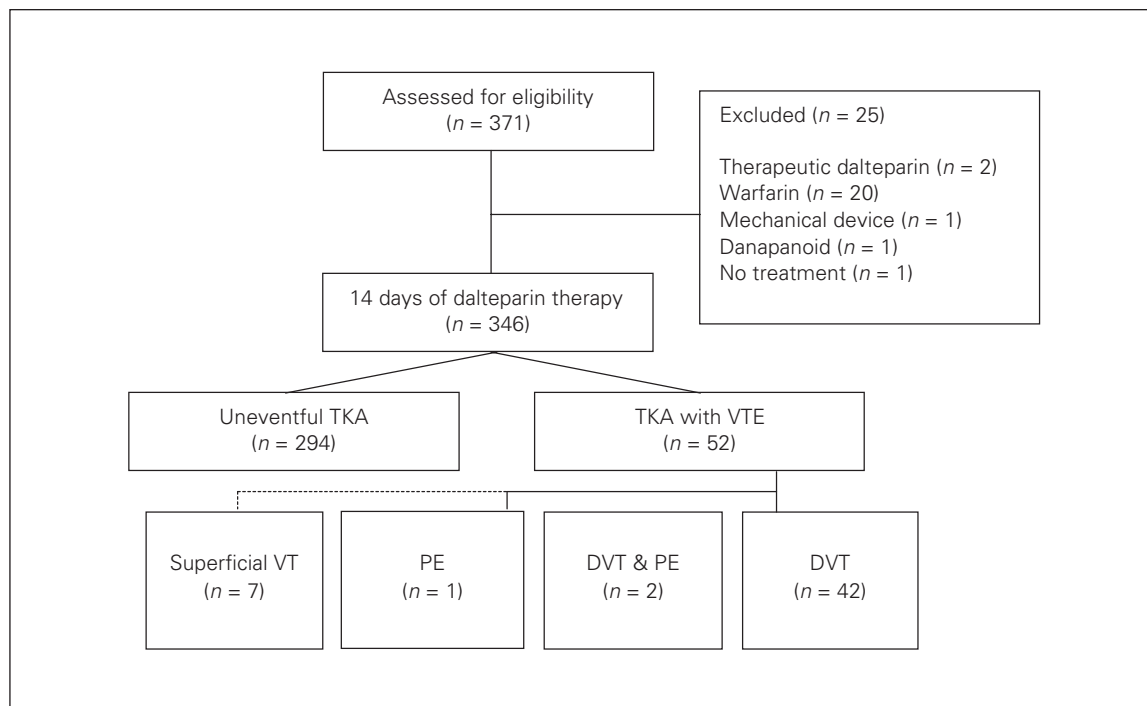


Fig. 1. Venous thromboembolic events (VTE) among patients in the study. DVT = deep vein thrombosis; PE = pulmonary embolism; TKA = total knee arthroplasty; VT = vein thrombosis.

our service. No thromboembolic events were noted in patients receiving tranexamic acid ($n = 12$) during TKA surgery. The application and duration of the tourniquet did not influence the incidence of VTE in either group ($p = 0.46$ and $p = 0.68$).

Delay of dalteparin administration after surgery was a significant risk factor for VTE in our study. The delay before receiving the first dose of dalteparin was 19.5 (range 10–48) hours in patients with no events and was 22.6 (range 11.5–52) hours among patients affected by a VTE ($p = 0.003$). This delay in receiving the first dalteparin dose could be explained by surgeons' prescription specifications without documented explanation. No clerical errors from the nursing staff were identified as a possible cause of delays in medication administration during the study period. The subgroup of patients who received their first dose of dalte-

parin within 12 h after surgery experienced a significantly lower rate of DVT and PE than the subgroup who received their first dose 24 h or more after surgery (8.5% v. 16.3%, $p = 0.048$). Table 3 shows that administering dalteparin 24 h after surgery did not decrease the risk of major bleeding. The subgroup of patients who had LMWH dose adjustments according to their body weight did not experience more bleeding events (Table 4) and experienced 50% fewer VTE (8.7% v. 16.3%; Table 1).

DISCUSSION

There is a wide disparity of thromboprophylaxis practices after orthopedic surgery, including variants in pharmaceutical drugs, mechanical devices, or a combination of both. Differences between thromboprophylaxis protocols

Table 1. Demographic and clinical characteristics of study patients

Characteristics	Group; no. (%) or mean \pm SD			95% CI	<i>p</i> value
	Global population, <i>n</i> = 346	With VTE, <i>n</i> = 52	No VTE, <i>n</i> = 294		
Female sex	216 (62.4)	38 (73.1)	178 (60.5)	0.29–1.09	0.09
Age, yr	66.8 \pm 10.2	66.1 \pm 10.8	67.0 \pm 10.1		0.55
Weight, kg	86.2 \pm 20.1	85.62 \pm 19.0	86.5 \pm 20.3		0.53
BMI	32.3 \pm 6.3	31.5 \pm 5.1	32.4 \pm 6.5		0.36
Type of surgery					0.52
Primary TKA	329 (95.1)	50 (96.2)	279 (94.9)		
Revision TKA	17 (4.9)	2 (3.9)	15 (5.1)		
Type of anesthesia					0.64
General	216 (62.4)	30 (57.7)	186 (63.3)		
Regional	127 (36.7)	20 (38.5)	107 (36.4)		
Both combined	3 (0.9)	2 (3.8)	1 (0.3)		
Tourniquet use	343 (99.1)	52 (100)	291 (99)		0.46
Tourniquet duration, min	91.6 \pm 22.5	90.4 \pm 21.6	91.8 \pm 22.7		0.68
Tranexamic acid use	12 (3.5)	0	12 (4.1)		0.14
LOS, d	8.6 \pm 4.0	11.2 \pm 5.4	8.2 \pm 3.5		< 0.001
≥ 2 units transfused	53 (15.3)	13 (25.0)	40 (13.6)		0.036
≥ 2 g/dL drop in hemoglobin	331 (95.7)	51 (98.1)	280 (95.2)		0.36
Risk factors					
History of previous VTE	29 (8.4)	7 (13.5)	22 (7.5)		0.15
HRT pre-op	34 (9.8)	15 (28.8)	19 (6.5)	0.85–6.89*	0.09
Noncessation of HRT 4 wk prior to surgery	19 (6.1)	6 (16.2)	13 (4.7)		
Thromboprophylaxis					
First dose of dalteparine post-op, h	20.0 \pm 7.0	22.6 \pm 9.0	19.5 \pm 6.6		0.003
Dalteparine initiation post-op					0.06
≤ 12 h post-op	133 (38.6)	14 (26.9%)	119 (40.6%)		
≥ 24 h post-op	212 (61.4)	38 (73.1%)	174 (59.4%)		
Dalteparine dosage, units	5375 \pm 1069	5192 \pm 835	5407 \pm 1103		0.18
Dalteparine dosage distribution					0.15
≤ 5000 units	289 (83.5)	47 (90.4)	242 (82.3)		
> 5000 units	57 (16.5)	5 (9.6)	52 (17.7)		
Dalteparine dosage/weight, units/kg	64.0 \pm 12.0	63.3 \pm 12.8	64.2 \pm 11.9		0.64
Dalteparine interruption	20 (5.8)	4 (7.7)	16 (5.4)		0.54

BMI = body mass index; CI = confidence interval; HRT = hormone replacement therapy; LOS = length of stay in hospital; SD = standard deviation; TKA = total knee arthroplasty; VTE = venous thromboembolic event.

*Odds ratio 2.4.

make studies on the subject difficult to compare directly. Our study highlights that LMWH given for 14 days after primary and revision TKA was safe and led to a proximal DVT rate of 1.7% and a nonfatal PE rate of 0.9%. Furthermore, LMWH dose adjustment according to body weight less than 45 kg or exceeding 100 kg proved safe, as this did not increase bleeding risks. The continuation of hormone replacement therapy until surgery and the dalteparin administration 24 h after surgery instead of within 12 h of surgery potentially increased the risk for VTE in our cohort.

Few studies have reported higher than average VTE rates. Guan and colleagues¹² obtained a 20% incidence of symptomatic VTE, while Kerr and Linkins⁶ reported a 4.6% incidence of PE. The incidence of symptomatic VTE at 3 months observed in our study (15%) was significantly higher than that reported in other studies,^{1,10} although it approached the VTE rate described by Guan and colleagues.¹² However, it should be noted that our incidence of PE (0.9%) and our proximal DVT rate (1.7%) were well within the values usually reported in studies of VTE post-TKA. The main difference in the literature consulted was that the incidence of DVT (12.7%) consisted mostly of distal DVT (11.0%). Only 1 other study¹³ has an incidence of DVT as high after reviewing 310 cases of orthopedic surgery, 92 of which were TKA. Although the rate of distal DVT post-TKA was higher than that observed at our centre (22.8% v. 11.0%), our rate of proximal DVT was lower than theirs, but to a lesser extent (3.2% v. 1.7%).¹³

Delaying the administration of postsurgical thromboprophylaxis increased the risk of VTE significantly in our cohort ($p = 0.003$). The subgroup of patients who received their first dose of dalteparin within 12 h after surgery presented with a significantly lower rate of DVT and PE than the subgroup who received their first dose 24 h or more after surgery ($p = 0.048$). Our VTE rate of 15% may have been influenced by the fact that thromboprophylaxis was administered a mean of 20 h after surgery. The actual time of LMWH administration after surgery is rarely reported, making comparisons among studies difficult. The mean delay in LMWH administration of 9 h after surgery in the study by Schiff and colleagues¹³ resulted in a DVT rate of 26% and no PE. The incidence of VTE was much lower (5.7%) in a study by Kerr and colleagues⁶ despite them having administered the first dose of LMWH the day after surgery. The rate of PE, however, was as high as 5% in that study.⁶ It is recognized that DVT often develops intraoperatively.¹⁴ Thromboprophylaxis could be less effective if it is initiated later, when the blood clot is forming. This argument is also supported by Warwick and Rosencher.¹⁵ However, the incidence of major and minor bleeding would have to be considered in the decision process, as it could be a limiting factor. The bleeding risk was the main concern of anesthesiologists

and surgeons participating in this study, and it was the main reason leading them to delay LMWH administration. Such worries may not have been warranted since no differences in major bleeding were shown when comparing the moment of administration of dalteparin (≤ 12 h v. ≥ 24 h after surgery). Minor bleeding was not analyzed in this study. We found no association between the timing of thromboprophylaxis administration and bleeding after surgery in the current literature. Since the completion of this study, the internal LMWH protocol has been revised to initiate LMWH thromboprophylaxis 12 h after TKA, with an interval of 24 h between the first 2 doses.¹⁶

Obesity is a risk factor identified in the literature,^{1,17} and a BMI above 30 is associated with a higher rate of DVT in the postoperative period.¹⁸ Obesity did not play a role in our study, nor in that of Samama and colleagues,⁵ but has been reported by Memtsoudis and colleagues¹⁹ and Guan and colleagues.¹² The mean weight of 86 kg and mean BMI of 32 in our cohort are similar to those reported in other studies on TKA.⁸ A fixed dose of dalteparin is usually recommended for DVT prophylaxis, regardless of weight or BMI, in contrast to the doses prescribed for the treatment of DVT. Kucher and colleagues²⁰ support this recommendation unless the patient has a BMI above 40. The 2008 ACCP guidelines suggest a dose based on weight for obese patients receiving LMWH prophylaxis or therapy (Grade

Table 2. Venous thromboembolic events characteristics, $n = 346$

Characteristic	No. (%) of patients or mean \pm SD
VTE incidence	52 (15.0)
VTE type	
Superficial vein thrombosis	7 (2.0)
DVT*	44 (12.7)
Distal*	38 (11.0)
Proximal	6 (1.7)
PE†	3 (0.9)
Nonfatal	3 (0.9)
Fatal	0
Delay in VTE detection, d post-op	
Global	5.6 \pm 3.9
Superficial vein thrombosis	10.0 \pm 6.7
DVT	5.0 \pm 2.9
PE	4.0 \pm 0
Investigation for VTE	
Doppler ultrasonography	120 (34.7)
Positive finding (out of 120)	51 (42.5)
Angio-CT or ventilation/perfusion lung scan	8 (2.3)
Positive finding (out of 8)	3 (37.5)
CT = computed tomography; DVT = deep vein thrombosis; PE = pulmonary embolism; SD = standard deviation; VTE = venous thromboembolic event.	
*Includes 2 patients with PE.	
†Diagnosed by lung ventilation/perfusion scans; 1 patient had CT pulmonary angiography for confirmation.	

Table 3. Bleeding events according to timing of first dalteparine dose

Bleeding events	Group; no. (%)			p value
	Global cohort, n = 345	First dalteparine dose ≤ 12 h post-op, n = 133	First dalteparine dose ≥ 24 h post-op, n = 212	
≥ 2 units transfused	53 (15.3)	18 (13.5)	35 (16.5)	0.46
Decrease ≥ 2 g/dL hemoglobin (pre-op v. post-op day 3)	330 (95.7)	125 (94.0)	205 (96.7)	0.23

Table 4. Bleeding events for patients 100 kg or heavier according to dalteparine dose

Bleeding events	Group; no. (%)			p value
	Patients ≥ 100 kg, n = 77	5000 units dalteparine, n = 24	> 5000 units dalteparine, n = 53	
≥ 2 units transfused	6 (7.8)	2 (8.3)	4 (7.6)	0.91
Decrease ≥ 2 g/dL hemoglobin (pre-op v. post-op day 3)	75 (97.4)	22 (91.7)	53 (100)	0.033

2C recommendation).²¹ Although not standardized, the practice in our centre is to increase the dose of dalteparin empirically by 50% when body weight is greater than 100 kg (i.e., 7500 units instead of the standard 5000 units of dalteparin). This may in itself explain why obesity was not identified as a risk factor in our patients. The fact that our obese patients did not experience more VTE and bleeding events may support this practice and help downplay the risk of thromboembolism in this subpopulation.

Limitations

The main limitation of this study was its retrospective design looking at risk factors gathered in a set of selected TKA patients. No patients were contacted to cross-reference risk factors, comorbidities or VTE possibly diagnosed after leaving the hospital. Therefore, the accuracy of evaluating nonstandard events, such as bleeding events, was diminished. The patients with complete data for inclusion in the study were those undergoing treatment in 1 of 3 local hospitals; a small but unknown number of patients may have been excluded from our analysis owing to incomplete data because they presented elsewhere with a VTE. In a larger study with a similar design and conducted in the same city, 1540 patient records were evaluated to confirm that no patients presented with a VTE at a different hospital than the one where the original surgery took place.²² We therefore assumed the patient flow would be similar in our cohort. Patients requiring long-term ASA were not analyzed in our study. In the context of such limitations, our results have to be interpreted with caution.

CONCLUSION

Although thromboprophylaxis with LMWH was systematically prescribed and administered routinely to patients undergoing TKA in this cohort, the observed VTE rate

was 15%. Delaying the administration of LMWH may have a deleterious impact on the VTE rate after TKA. A prompt initiation of LMWH (≤ 12 h after surgery) is more appropriate and does not increase the risk of major bleeding. Increasing the LMWH thromboprophylaxis dose in patients heavier than 100 kg was safe with comparable bleeding and VTE risks. New anticoagulants, such as rivaroxaban, apixaban and dabigatran, can represent another avenue to reduce the incidence of VTE in our patients admitted for elective primary and revision TKA. The influence of thromboprophylaxis administration timing after surgery must be considered in future analyses, ideally in a prospective study.

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Contributors: S. Plante, D. Fréchette and J. Lefebvre designed the study. S. Plante and D. Fréchette acquired the data, which all authors analyzed. S. Plante, E. Belzile and D. Fréchette wrote the article, which all authors reviewed and approved for publication.

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